(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2003 (13.02.2003)

PCT

(10) International Publication Number
WO 03/011859 A2

(51) International Patent Classification[7]: C07D 413/04, 413/12, 417/12, A61K 31/422, 31/427, 31/506, A61P 31/04

(21) International Application Number: PCT/GB02/03404

(22) International Filing Date: 25 July 2002 (25.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0118407.6 27 July 2001 (27.07.2001) GB

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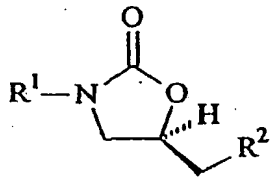
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OXAZOLIDINONE DERIVATIVES AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: Antibacterial oxazolidine compounds having the general formula (I) wherein R^1 comprises at least one substituted or unsubstituted phenyl group and at least one substituted or unsubstituted unsaturated heterocyclic group having two or more heteroatoms; and R^2 is an alkylidene, alkyl, halogen, alkanoyloxy, phosphate, substituted aryl sulphonate, ammonium, or imide group, a saturated or unsaturated heterocycle, H, OR^3, N_3 or NHR^4, wherein R^3=H, C_1-C_4 alkyl, SO_2 (C_1-C_4) alkyl, R^4=H, C_1-C_4 alkyl, C(=0)(C_1-C_4) alkyl.

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OXAZOLIDINONE DERIVATIVES AS ANTIBACTERIAL AGENTS

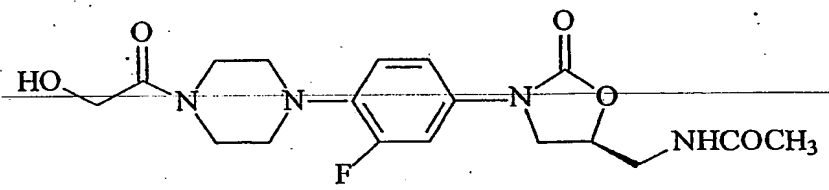
The present invention relates to novel oxazolidinone derivatives useful as antibacterial agents, and to their preparation.

Since the discovery of penicillin, pharmaceutical companies have produced more than a hundred antibacterial agents and antibiotics to combat a wide variety of bacterial infections. The major classes of antibacterial agents are β -lactams (including penicillins, cephalosporins, monobactams, carbapenems), aminoglycosides, tetracyclines, sulphonamides, macrolides (such as erythromycin), quinolones and glycopeptides (e.g. vancomycin). By the 1980s, with the use of these antibacterial agents, approved sanitary conditions and the extensive refrigeration of food, it was believed that industrialized nations had won the war against pathogenic microbes. However, in the past several years, the rapid emergence of bacterial resistance to antibiotics has been observed. The extensive use (and misuse) of antibiotics has provided powerful forces for the selection of microbes that either carried mutations conferring resistance, or had the enhanced ability to mutate to resistance in the face of the antibiotic. Bacteria have mutated or have acquired new genes producing new ways to overcome the action of many antibiotics. In recent years, many new antibiotic-resistant strains have been isolated from patients throughout the world.

The emergence of bacterial resistance to a number of antimicrobial agents such as β -lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major worldwide health problem. Particularly alarming is the emergence of *Staphylococcal* strains with reduced susceptibility to vancomycin, the so-called vancomycin glycopeptide intermediate strains (VISA or GISA). Thus, the search for novel potent broad spectrum antibacterial agents is being fervently pursued by pharmaceutical houses worldwide.

The totally synthetic oxazolidinones typified by eperezolid (1) and linezolid (2) are one such class of antibacterial agents with potent activity against gram-positive

organisms including MRSA, MRSE and VRE. They have been shown to selectively and uniquely bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis (Lin et al, 1997, Antimicrob. Agents Chemother. (41) 2127-2131 and Shinabarger et al 1997, Antimicrob. Agents Chemother. (41) 2132-2136).



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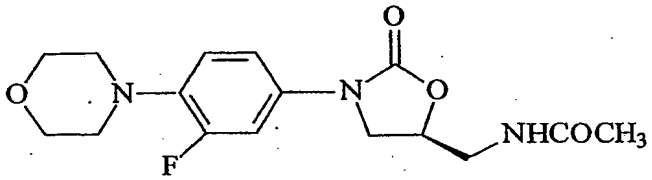
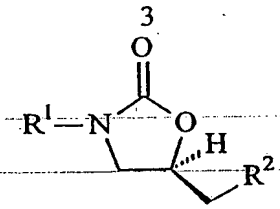


2

In addition, single step selection studies have demonstrated that eperezolid and linezolid-resistant mutants develop with a very low spontaneous mutation frequency of $<10^{-9}$ among selected *staphylococcal* bacteria (Zurenko et al 1996, Antimicrob. Agents Chemother. (40) 839-854).

We have realised that oxazolidinones have excellent potential to address the imminent critical need for new antibacterial agents. Using a predictive three-dimensional quantitative structure-activity relationship (3D-QSAR) model employing the genetic function approximation algorithm (GFA) in Cerius2, which we developed, we have designed and synthesized novel oxazolidinone compounds useful as antibacterial agents. In particular, we have made some new oxazolidinone derivatives which improve upon the properties of linezolid and eperezolid useful as antibacterial agents.

According to the present invention there is provided a compound of the general formula

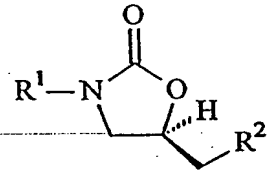


wherein R^1 comprises at least one substituted or unsubstituted phenyl group and at least one substituted or unsubstituted unsaturated heterocyclic group having two or more heteroatoms; and R^2 is an alkylidene, alkyl, halogen, alkanoyloxy, phosphate, substituted aryl sulphonate, ammonium, or imide group, a saturated or unsaturated heterocycle, H, OR^3, N_3 or NHR^4,

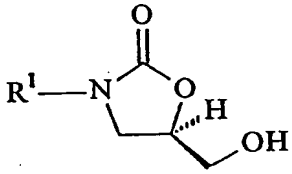
wherein R^3 = H, C_1-C_4 alkyl, SO_2 (C_1-C_4) alkyl

R^4 = H, C_1-C_4 alkyl, C (= O)(C_1-C_4) alkyl.

According to the present invention there is also provided a method of making a compound of the general formula

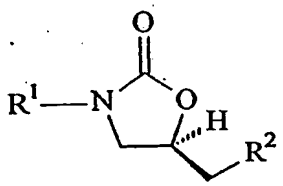


which method comprises the steps of deprotonating a carbamate of formula R^1-$NHCOOCH_2CH_3$, wherein R^1 is as defined above; and reacting the deprotonated carbamate with an (R)-glycidyl ester to produce a compound of formula



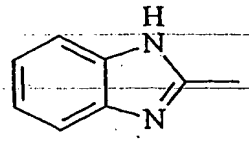
and optionally converting the OH group to OR^3, N_3 or NHR^4 wherein R^3 is C_1-C_4 alkyl or SO_2(C_1-C_4)alkyl and R^4 is as defined above.

Preferred compounds of the invention, include those of formula

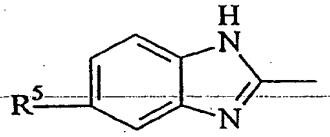


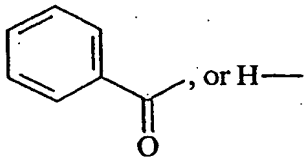
wherein R^1 comprises a phenyl group condensed with an unsaturated heterocyclic group,

Preferably, R^1 comprises a group of formula



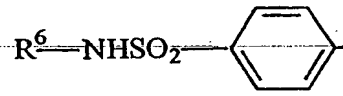
In a further preferred embodiment of the invention, R^1 comprises



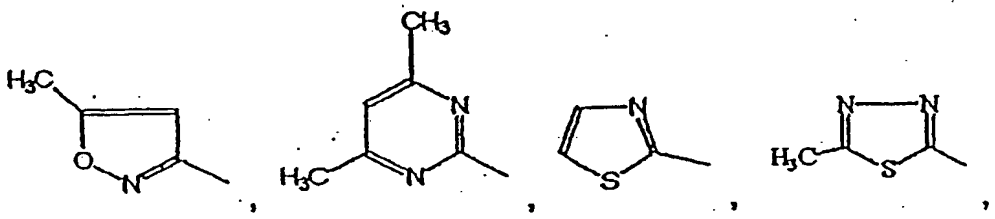
wherein R^5 is $H_3CH_2CH_2CS$-,  , or H—

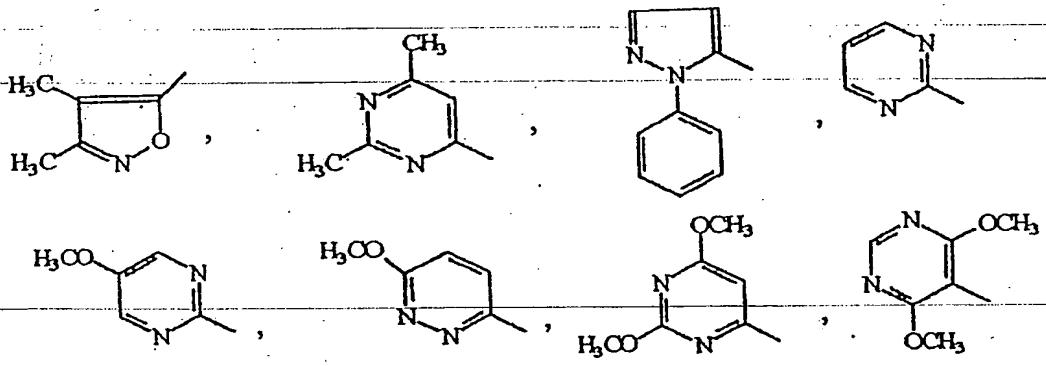
In an alternative preferred embodiment of the invention, R^1 comprises a phenyl group and an unsaturated heterocyclic group which are not condensed.

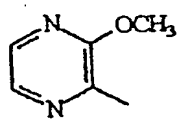
Preferably, the phenyl and unsaturated heterocyclic groups of R^1 are separated by an $NHSO_2$ group. Examples of such R^1 groups include those represented by the formula



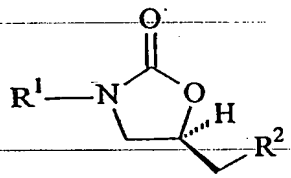
wherein R^6 can be





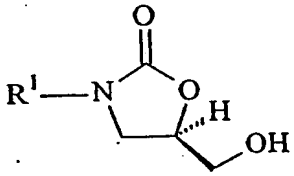
or 

As described above, the method of the present invention produces a compound of formula



wherein R^2 is -OH and R^1 is as defined above.

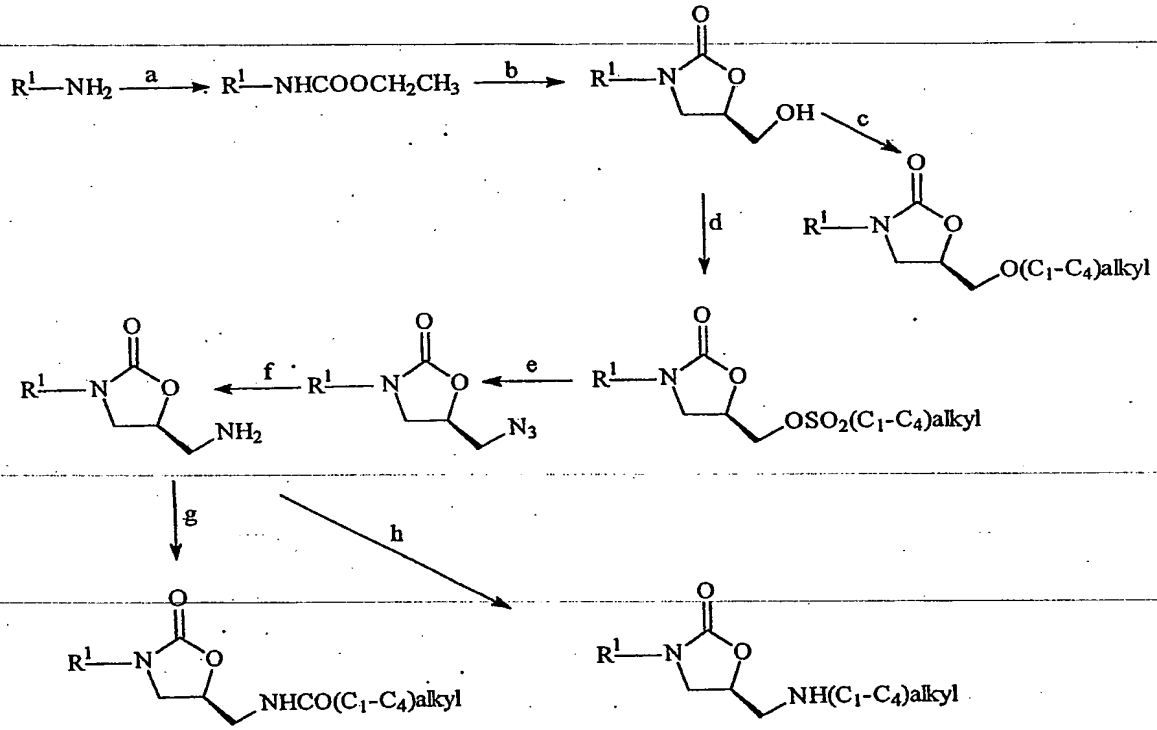
According to the method of the present invention, the (5R)-(hydroxymethyl)-2-oxazolidinone of formula



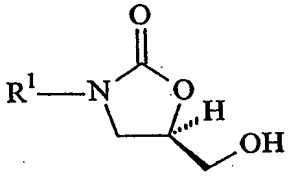
can be produced by deprotonating the carbamate of formula R^1-NHCOOCH$_2$CH$_3$ with, for example, sodium methoxide and reacting the deprotonated carbamate with an (R)-glycidyl ester. The carbamate can be produced from its corresponding amine of formula R^1-NH$_2$ by reaction with ethylchloroformate. The use of ethyl chloroformate and sodium methoxide, instead of benzyl chloroformate and butyl lithium, has made production of the (5R)-(hydroxymethyl)-2-oxazolidinone economical.

To give further compounds of the invention, the R^2 group of the (5R)-(hydroxymethyl)-2-oxazolidinone can be converted, independently of the R^1 group, from -OH to OR^3, N_3 or NHR^4, wherein R^3 is C_1-C_4 alkyl or $SO_2(C_1$-$C_4)$alkyl and R^4 is H, C_1-C_4 alkyl or $C(=O)(C_1$-$C_4)$alkyl. This conversion proceeds by means of a step-wise process, as set out in Scheme 1.

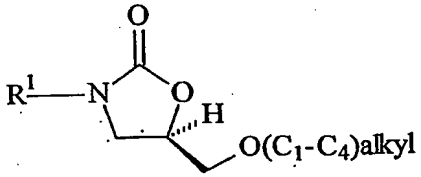
Scheme I



With reference to Scheme 1: The produced compound of formula

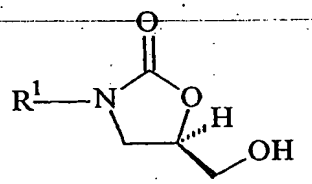


can be alkylated to produce a compound of formula

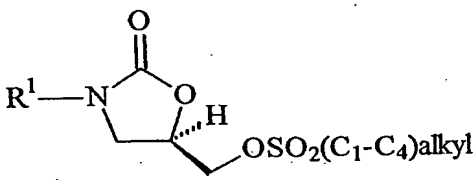


(step c)

Alternatively, reaction of a compound of formula

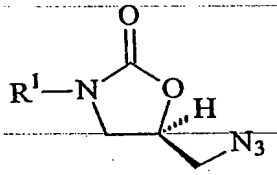


with an alkanesulphonyl chloride converts the alcohol to a salt of formula



(step d)

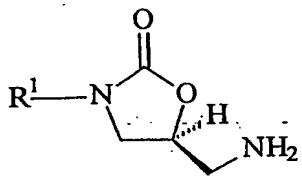
The alkylsulphonate can be displaced by reaction with an azide such as NaN_3 to produce an azide of formula



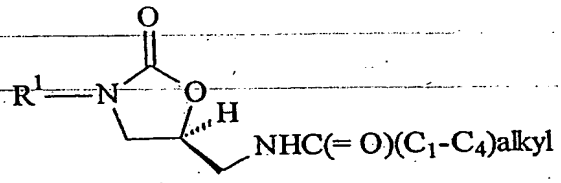
(step e)

The N_3 group of this latter compound can be converted to an amine group by catalytic hydrogenation (step f).

The resultant amine of formula

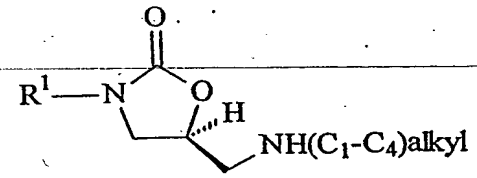


can be acetylated by, for example, treatment with acetic anhydride and pyridine, to produce a 5-(acetamidomethyl)-2-oxazolidinone of formula



(step g)

Alternatively, the amine can be alkylated to produce a compound of formula



(step h)

In order to further illustrate the invention without limiting its scope, the following Examples are given:

Examples

The compounds VMRG 1 through VMRG 19 were synthesised as described below and are shown in Table 1. Melting points were determined in capillary tubes and are uncorrected. Infrared spectra was recorded in KBr disks with Buck Scientific M-500 spectrophotometer and are reported in reciprocal centimeters. ^{1}H-NMR spectra were determined in the indicated solvent on a Varian 60 MHz NMR spectrometer and are reported in δ units (parts per million downfield from tetramethyl silane as the internal reference). Splitting patterns are designated as follows: s, singlet; d, doublet; t , triplet; q, quartet; m, multiplet; br, broad. Thin layer chromatography was performed on pre-coated aluminium sheets coated with Silica Gel 60 F_{254}, 0.2 mm thickness.

Synthesis of 2-carboethoxyamino-5-(propylthio)benzimidazole:

To a solution of 5 g (0.022M) of 2-amino-5-(propylthio)benzimidazole and 3.7 g (0.044M) of sodium bicarbonate in 100 ml of acetone and 50 ml of water at 0° C was added 3.78 g (0.033M) of ethyl chloroformate. After stirring the mixture for 2 hrs, the mixture was poured on to 500 cc of ice and water and the ice allowed to melt. The precipitated solid was collected by filtration and washed with water and dried in vacuum oven at 60° C to give a white solid (5.87 g). The product was utilized without purification for the next reaction.

Yield = 87.09 %

Synthesis of (R)-N-[3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methanol (VMRG 1):

In a 500 ml 3-necked flask fitted with a mechanical stirrer, a reflux condenser and a thermometer pocket 2.90 g (0.0538M) of sodium methoxide was dissolved in 100 ml of methanol cooled to 0° C. To this solution 5g (0.0179M) of 2-carboethoxyamino-5-(propylthio)benzimidazole was added at 0°C and stirred for 20 min. To this 3.88 g (0.0269M) of R-glycidyl butyrate was added and after 1 hour the flask was removed from the ice-bath. The temperature was gradually raised and the reaction mixture was refluxed for 4 hours. It was then cooled to room temperature. To this 100 ml of saturated aqueous ammonium chloride was added followed by 100 ml of water. A pale pink coloured solid was precipitated. The mixture was filtered and washed with water. It was chromatographed on silica using as eluant a gradient increasing in polarity from 0 to 5% methanol in chloroform to give (R)-N-[3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methanol, 3.74 g (67.94 %).

Melting point: 168 -170°C

^{1}H-NMR(DMSO-*d6*) δ 1.00 (t, 3H, CH_3); 1.3-1.8 (sextet, 2H, CH_2); 2.9 (t, 2H, CH_2); 3.8 (s, 2H, ring CH_2); 4.2-4.3 (3H, CH_2 and OH merged); 4.8 (m, 1H, ring CH); 7.1-7.6 (m, 3H, aromatic H) I. R. 3332.6 (br, -OH stretching), 3119.8 (aromatic CH stretching), 1678.7 (ring C=O)

Mass 307

Rf = 0.54 (10: 1 Chloroform/methanol, v/v)

Synthesis of (R)-N- [3-[5-(propylthio)benzimidazolyl]-2-oxo-oxazolidinyl]methane-sulphonate (VMRG 2):

To a solution of 2 g (0.0065 M) of (R)-N-[3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methanol and 0.66 g (0.0065 M) of triethylamine in 25 ml of methylene chloride at 0°C under nitrogen, 0.89 g (0.0073 M) of methanesulphonyl chloride was added over 5 minutes. The mixture was allowed to stir at 0°C for 30 minutes, then allowed to warm to ambient temperature. The reaction mixture was stirred at 40°C for 4 hours. The reaction mixture was cooled to room temperature and then slowly poured on to crushed ice. The precipitated solid was filtered. The filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with brine solution, dried over anhydrous

sodium sulphate and the solvent removed under reduced pressure to give a brown coloured solid. The mixture was purified by chromatography on a silica gel column, eluting with a gradient of 5-10% chloroform/methanol (v/v); the combined proper fractions gave a cream colored crystalline powder, 1.36 g (54.23 %).

Melting point: 152-154°C

^{1}H-NMR(DMSO-*d6*) δ 1.00 (t, 3H, CH_3); 1.3-1.8 (sextet, 2H, CH_2); 2.8 (t, 2H, CH_2); 3.2 (s, 3H, CH_3); 3.6 (m, 4H, CH_2), 4.0 (1H, ring CH); 7.1-7.7 (m, 3H, aromatic H)

I.R. 3375.1 (aromatic CH stretching), 1751.8 (ring C=O), 1411.3 and 1241 (SO_2 stretching)

Mass 385

Rf = 0.68 (Chloroform)

Synthesis of (R)-N-[3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methyl azide (VMRG 3):

To a solution of 1 G (0.0026 M) of (R)-N-[3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methanesulphonate in 20 ml of dimethylformamide 0.186 g (0.00286 M) of sodium azide was added and the mixture heated at 85 °C for 8 hours. The mixture was cooled and poured into crushed ice. The precipitated solid was filtered and dried in a vacuum oven.

Melting point: 88-90 °C

^{1}H-NMR(DMSO-*d6*) δ 1.00 (t, 3H, CH_3); 1.5-2.0 (sextet, 2H, CH_2); 3.0 (t, 2H, CH_2); 3.7 (s, 2H, ring CH_2); 4.2 (t, 2H, CH_2); 4.9 (m, 1H, ring CH); 7.0-7.6 (m, 3H, aromatic H)

Mass 332

Rf = 0.77 (10:1 Chloroform/methanol, v/v)

Synthesis of (S)-N- [3-[5-(propylthio)benzimidazolyl]-2-oxo-5-oxazolidinyl]methyl acetamide (VMRG 4):

To a solution of 0.920 g (0.0028 M) of (R)-N-[3-[5-propylthiobenzimidazolyl]-2-oxo-5-oxazolidinyl]methyl azide (the crude product was used without purification) in 100 ml ethyl acetate 0.1 g of 10% palladium/carbon was added. The flask was evacuated and filled with nitrogen. It was then evacuated and filled with hydrogen. The mixture was then stirred at 50°C under 50 psi pressure for 24 hours. This reaction was carried out

using a Parr hydrogenator device. The reaction mixture was filtered, washing the residue with ethyl acetate. The filtrate was concentrated under vacuo to give a brown gummy solid (0.850 g, 0.0028 M). This was dissolved in 50 ml ethylacetate. To this 0.23 g (0.0028 M) pyridine and 0.280 g (0.0028 M) acetic anhydride was added and stirred at room temperature for 4 hours. The reaction mixture was washed with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a brown gummy solid. The mixture was purified by chromatography on a silica gel column, eluting with a gradient of 5-10 % chloroform/methanol , (v/v); the combined proper fractions gave a cream colored solid 0.7 g (72.39 %).

Melting point: 112-114 °C

^{1}H-NMR(DMSO-*d6*) δ 0.9 (t, 3H, CH_3); 1.5 (2H, CH_2); 1.9 (m, 2H, CH_2); 2.6 (3H, CH_3); 3.5 (2H, CH_2), 4.2 (2H, CH_2); 4.8 (1H, CH); 7.3 (m, 3H, aromatic H); 11.0 (s, 1H, NH)

I.R. 3375.1 (NH stretching), 3271.8 (aromatic CH stretching), 1739.5 (amide C=O), 1654.5 (ring C=O)

Mass 348

Rf = 0.51 (10:1Choroform/methanol, v/v)

Compounds VMRG 5-VMRG 19 were synthesized as above. The melting point of these compounds is reported in Table I.

Biological Evaluation

The compounds (VMRG 1-VMRG 19) were screened for antibacterial activity against *Staphylococcus aureus* ATCC 29213. The biological activity data is summarised in Table 1.

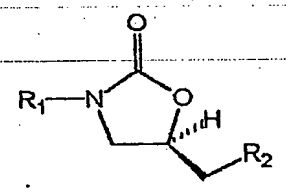
A stock solution of the compound was prepared using dimethyl sulphoxide and sterile water. The volume of dimethyl sulphoxide used, varied from 0.1 ml to 0.5 ml depending upon the solubility of the compound. The concentration of the stock solution was 1000 µg/ml. Different dilutions of the sample solution were prepared by serial dilution of the stock solution. To 9 ml of sterile nutrient broth taken in a test tube, 1 ml of sample solution was added followed by 0.1 ml of *Staphylococcus aureus* ATCC 29213 culture (corresponding to $5x10^5$ CFU/ml). The compounds were tested at 100, 10, 1 and 0.1 µg/ml concentrations in duplicate. The tubes were incubated at 37 °C for 48 hours. A set

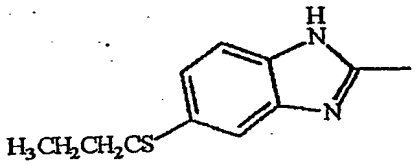
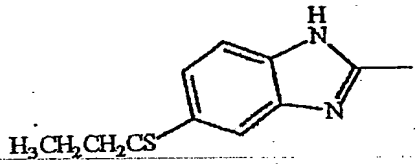
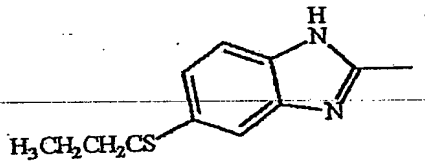
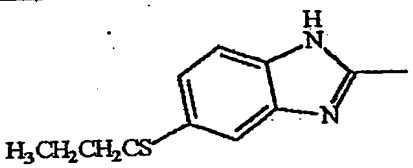
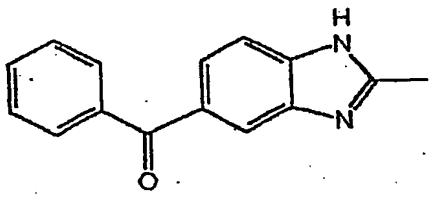
of negative and positive control of growth was also kept for incubation along with the sample tubes. In the tube for negative growth, 1 ml of sterile water was added instead of the sample solution and no culture was added while in the tube representing maximum growth (positive control) 1 ml of sterile water was added followed by 0.1 ml of the culture. The optical densities of the solutions were measured using negative control as the blank at λ 490 and 520, after 24 and 48 hours of incubation. Minimum inhibitory concentration was taken as the minimum concentration of the compound at which the optical density is the same as the negative control indicating complete inhibition of growth.

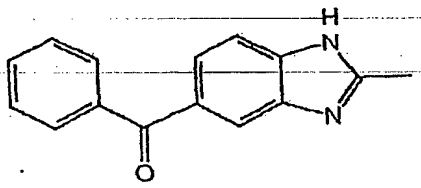
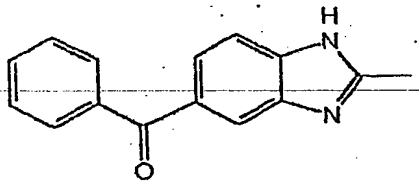
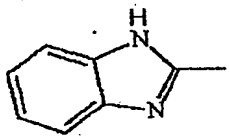
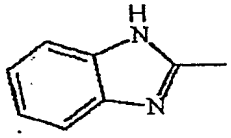
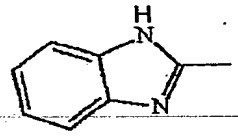
Summary

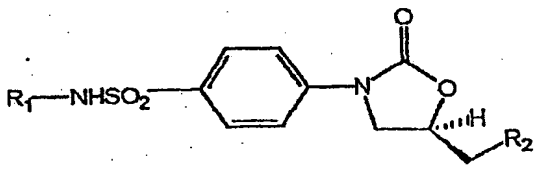
Compounds of the invention show promising antibacterial activity. They thus represent new leads in the search for new antibacterial agents, and warrant further study.

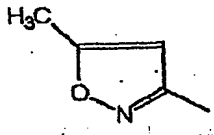
Table I: Structures, Melting point and biological activity data of the compounds synthesized

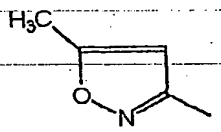
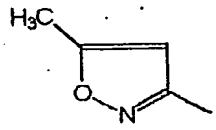
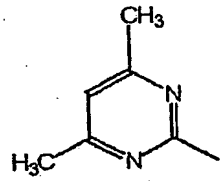
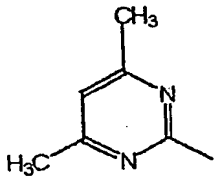
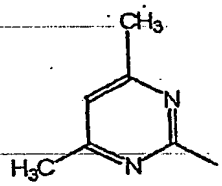
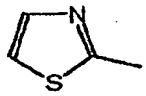
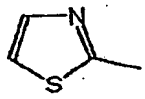
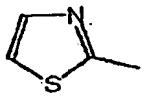


Compound Name	R_1	R_2	Melting Point °C	Biological Activity [a]
VMRG 1		-OH	168-170	< 1 μg/ml
VMRG 2		$-OSO_2CH_3$	152-154	< 1 μg/ml
VMRG 3		$-N_3$	88-90	>100 μg/ml
VMRG 4		$-NHCOCH_3$	112-114	>100 μg/ml
VMRG 5		-OH	120-122	< 1 μg/ml

VMRG 6		$-OSO_2CH_3$	190-192	≥100 μg/ml
VMRG 7		$-NHCOCH_3$	154-156	≥ 100 μg/ml
VMRG 8		-OH	194-196	≥ 100 μg/ml
VMRG 9		$-OSO_2CH_3$	212-214	> 100 μg/ml
VMRG 10		$-NHCOCH_3$	174-176	> 100 μg/ml



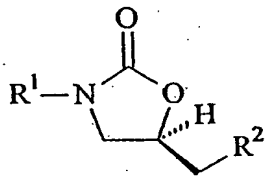
Compound Name	R_1	R_2	Melting Point °C	Biological Activity
VMRG 11		-OH	232-235	< 1 μg/ml

VMRG 12		$-OSO_2CH_3$	218-220	>100 µg/ml.
VMRG 13		$-NHCOCH_3$	162-164	> 100 µg/ml
VMRG 14		-OH	220-222	> 100 µg/ml
VMRG 15		$-OSO_2CH_3$	215-218	< 1 µg/ml
VMRG 16		$-NHCOCH_3$	158-160	> 100 µg/ml
VMRG 17		-OH	> 230	Not active at 100 µg/ml
VMRG 18		$-OSO_2CH_3$	> 230	> 100 µg/ml
VMRG 19		$-NHCOCH_3$	198-200	> 100 µg/ml

[a] Minium inhibitory concentration determined by tube dilution method on *Staphylococcus aureus* ATCC 29213. MIC of Linezolid by this method was found to be 1µg/ml.

CLAIMS:

1. A compound of the general formula



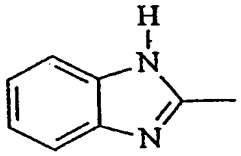
wherein R^1 comprises at least one substituted or unsubstituted phenyl group and at least one substituted or unsubstituted unsaturated heterocyclic group having two or more heteroatoms; and R^2 is an alkylidene, alkyl, halogen, alkanoyloxy, phosphate, substituted aryl sulphonate, ammonium, or imide group, a saturated or unsaturated heterocycle, H, OR^3, N_3 or NHR^4,

wherein R^3 = H, C_1-C_4 alkyl, SO_2 (C_1-C_4) alkyl

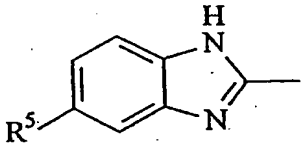
R^4 = H, C_1-C_4 alkyl, C (= O)(C_1-C_4) alkyl.

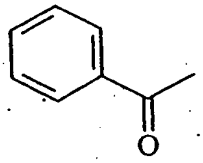
2. A compound according to claim 1, wherein R^1 comprises a phenyl group condensed with an unsaturated heterocyclic group.

3. A compound according to claim 2, wherein R^1 comprises a group of formula



4. A compound according to claim 1, 2 or 3, wherein R^1 is

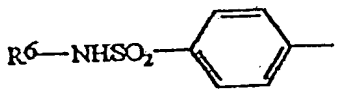


wherein R^5 is $H_3CH_2CH_2CS$-,  or H-

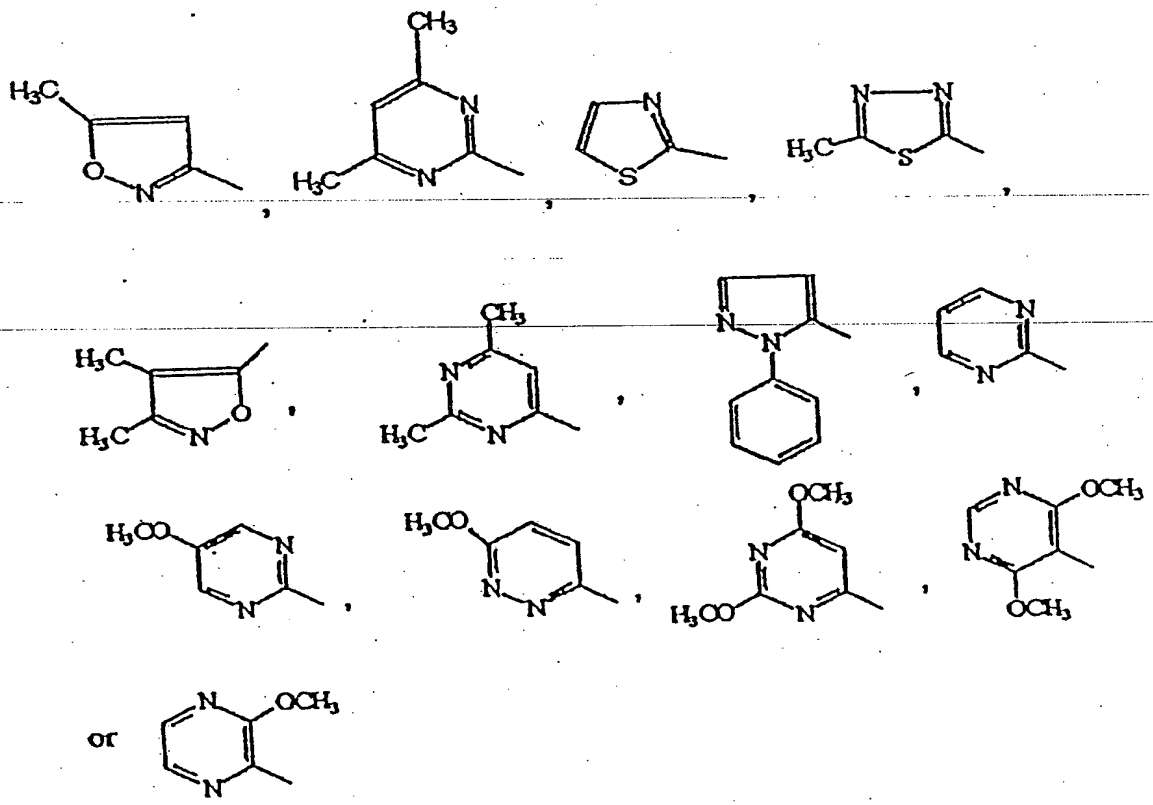
5. A compound according to claim 1, wherein the phenyl group and the unsaturated heterocyclic group of R^1 are not condensed.

6. A compound according to claim 5, wherein the phenyl group and the unsaturated heterocyclic groups of R^1 are separated by an $-NHSO_2-$ group.

7. A compound according to claim 5 or 6, wherein R^1 - has the formula:



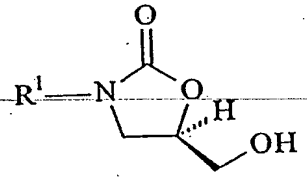
wherein R^6 is



or

8. A method of making a compound according to claim 1, which method comprises the steps of:

deprotonating a carbamate of formula $R^1NHCOOCH_2CH_3$, wherein R^1 is as defined in claim 1, and reacting the deprotonated carbamate with an (R)-glycidyl ester to produce a compound of formula:



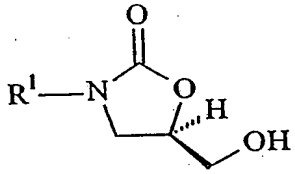
and optionally converting the OH group to OR^3, N_3 or NHR^4

wherein $R^3 = C_1$-C_4 alkyl,$SO_2(C_1$-$C_4)$alkyl

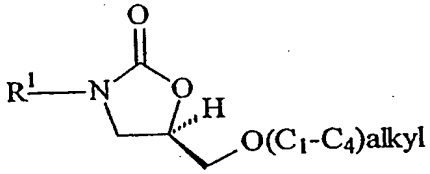
$R^4 = H$, C_1-C_4 alkyl,$C(=O)(C_1$-$C_4)$alkyl.

9. A method according to claim 8, in which said carbamate is produced by reacting an amine of formula R^1-NH_2, wherein R^1 is the same as in said carbamate, with ethyl chloroformate.

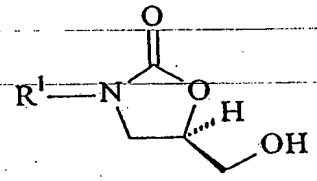
10. A method according to claim 8 or 9, in which said compound of formula



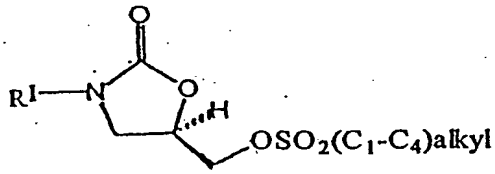
is alkylated to produce a compound of formula



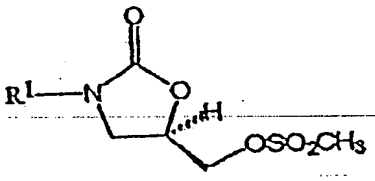
11. A method according to claim 8 or 9, in which said compound of formula



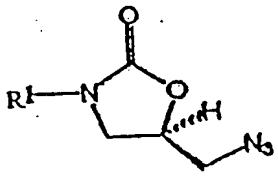
is reacted with alkanesulphonyl chloride (e.g. methanesulphonyl chloride) to produce a compound of formula



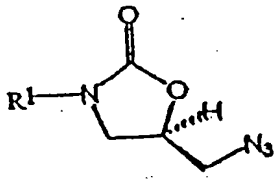
12. A method according to claim 11, in which said compound of formula



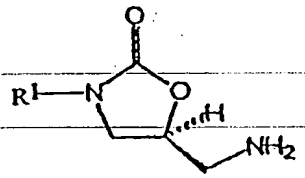
is reacted with an azide to produce a compound of formula



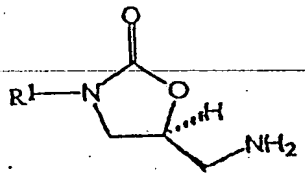
13. A method according to claim 12, in which said compound of formula



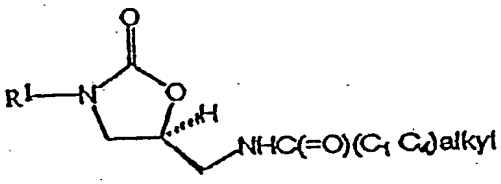
is reduced to a compound of formula



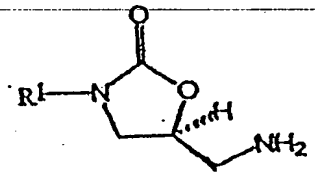
14. A method according to claim 13, in which said compound of formula



is acetylated to produce a compound of formula



15 A method according to claim 13, in which said compound of formula



is alkylated to produce compound of formula